REMARKS

Claims 32-40 are all the claims pending in the application, and all of the claims are currently rejected.

I. Claim Rejections Under 35 U.S.C. § 103(a)

At page 2 of the Office Action, claims 32-40 are rejected under 35 U.S.C. § 103(a) as being obvious over Jackson et al. (US 2002/0164374) in view of Bosca et al. (Age, 1997), Deshpande et al. (Med. Sci. Res., 1997), and Quiles et al. (BioFactors, 1998), with evidence provided by Tsuda et al. (Atherosclerosis, 1996).

Specifically, the Examiner states that Jackson teaches a pharmaceutical composition containing curcumin as an active ingredient for treating vascular diseases including atherosclerosis, and that Jackson teaches that local concentrations of fibrinogen increase as part of the chain of events leading to the formation of obstructive atherosclerotic vascular plaques and narrowing of the vessels. The Examiner further states that Bosca, Deshpande, and Quiles teach the administration of an aqueous alcoholic extract of *Curcuma longa* rhizomes to humans or to rabbits, and teach that such extracts are useful for treating and/or preventing coronary heart disease, such as arteriosclerosis. The Examiner contends that Tsuda teaches that elevated plasma fibrinogen is known to progress to atherosclerosis (an extremely common form of arteriosclerosis) and to be one of the risk factors for the occurrence of cardiovascular disease. The Examiner thus concludes that it would have been obvious to administer the curcumin-containing pharmaceutical composition taught by Jackson to a subject suffering from a

cardiovascular disease, such as atherosclerosis, including atherosclerosis involving vascular plaque formation related to elevated fibrinogen levels.

The Examiner states that Applicants' arguments filed in the November 17, 2003 Amendment with respect to the § 103 rejection, have been carefully considered but were not found persuasive. In the November 17, 2003 Amendment, Applicants submitted that since Jackson only suggests curcumin's antioxidant, hypolipedemic, and hypercholesterolemic properties, it would not have been obvious to administer the curcumin-containing pharmaceutical composition taught by Jackson to reduce fibrinogen levels. The Examiner responds that the express teachings of Jackson with respect to the well-known correlation between fibrinogen concentrations and the formation of atherosclerotic plaques, does not suggest precluding treatment of atherosclerosis caused by elevated plasma fibrinogen levels with curcumin. Further, the Examiner responds that the art as a whole would not lead one of ordinary skill in the art to preclude treating atherosclerosis with curcumin, whatever the underlying cause(s) thereof, including atherosclerosis caused by increased plasma fibrinogen concentrations.

II. Response to 35 U.S.C. § 103 Rejection

Applicants respectfully traverse the rejection under 35 U.S.C. § 103(a). Applicants submit that the Examiner has applied an improper legal standard of obviousness, and as such, Applicants respectfully request that this rejection be withdrawn.

MPEP § 2142 states that, to establish a *prima facie* case of obviousness, the prior art must teach or suggest all claim limitations, together with a suggestion to modify or combine these

teachings with a reasonable expectation of success. Applicants submit that, for the following reasons, the Examiner has not met this burden.

While *Curcuma* is known to have several pharmacological activities related to atherosclerosis and vascular disease, such as, for example, as an antioxidant, LDL reducer, and lipidic peroxide reducer, Applicants assert that none of the cited references teach or suggest that any compound of *Curcuma* is effective to reduce fibrinogen levels. Further, the Examiner has not provided a suggestion to combine the teachings of Jackson with respect to Curcumin's antioxidant, hypolipedemic, and hypercholesterolemic properties, with the teachings of Tsuda, with respect to the relationship between elevated fibrinogen levels and atheroscelerosis.

The Examiner states at page 4 of the February 17, 2004 Office Action, that the prior art does not "preclude" treatment of atherosclerosis caused by elevated fibrinogen levels with *Curcuma*. However, stating that the prior art does not "preclude" the invention is not a suggestion or motivation to combine the teachings of the references, and as such, the Examiner has applied an improper legal standard of obviousness. Accordingly, Applicants respectfully request that this rejection be withdrawn.

In addition, Applicants' submit that the prior art does not teach or suggest that *Curcuma* can be effective to reduce fibrinogen levels. The fact that *Curcuma* has pharmacological activities as an antioxidant, hypolipedemic, and hypercholesterolemic, as taught by Jackson, does not suggest any activity of *Curcuma* with respect to fibrinogen levels, since a drug capable of reducing one risk factor for atherosclerosis does not imply that the drug reduces any other risk factor(s).

In fact, several compounds were known in the art that affect parameters related to cardiovascular diseases or atherosclerosis, and such compounds have unpredictable effects on fibrinogen levels (i.e. fibrinogen levels are an independent risk factor for cardiovascular disease). As taught by Applicants' specification at page 9:

> Vitamin C and vitamin E, drugs that gave antioxidant and lipidic peroxid reducing properties, have had no effect on the plasmatic concentration of fibrinogen in humans after their administration. (Bates et al J Hypertens. Jul; 16 (7): 925-32 (1998)). Moghadasian et al Circulation Apr 6; 99 (13): 1733-1739 (1999) conclude that the probucol, which is known to have hypolipemiant and antioxidant capacity, increases the plasmatic concentrations of fibrinogen, showing proatherogenic activity. Rifici et al Thromb Haemost Sep; 78 (3): 1111-4 (1997) show that the lipooxidation produced by antioxidant vitamins does not alter the fibrinolitic activity.

Further, Song and White in *Ann Pharmacother.* (2001 Feb, 35(2):236-41), abstract attached herewith, disclose the effects of various statins, hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, on fibrinogen. Statins are known for their lipid lowering properties and are currently used for the treatment of vascular diseases. Song and White determined that: (1) Atorvastatin induces significant increases in fibrinogen, (2) Lovastatin induces significant increases in fibrinogen, Simvastatin has a neutral effect on fibrinogen, and Pravastatin decreases fibrinogen (7-19%). Thus, while Altorvastatin, Lovastatin, Simvastatin, and Pravastatin are all used for the treatment of vascular disease, only Pravastatin significantly decreases fibrinogen

concentration in plasma. Therefore, the skilled artesian, as of the Application's priority date, could not have predicted the effects of any drug on fibrinogen levels based upon that drugs effects on other parameters related to cardiovascular disease, because fibrinogen levels are an unrelated risk factor.

Moreover, Curcuma extract reduces fibrinogen levels by an amount unexpected based on the prior art. Song and White have disclosed a reduction in fibrinogen concentrations with pravastatin of 7-19%, and a reduction of only 17% when starting with pathological values of fibrinogen. On the other hand, Curcuma extract reduces fibrinogen concentration in plasma by 19% (in Example 1, page 16 of the specification; mean value at t=0: 317; mean value at day 30 after treatment: 257). This reduction with curcuma is much greater when considering only the pathological values, for instance: from 809 to 241 (23rd entry, Example 1), from 690 to 240 (27th entry, Example 1) or from 584 to 290 (28th entry, Table 1). The mean reduction in fibrinogen levels for the pathological starting values (i.e. the reduction in fibrinogen level/starting value) is therefore 62%, versus 17% for pravastatin as shown by Song and White. Therefore, the present invention produces unexpectedly superior results, and as such, is not obvious. Accordingly, Applicants respectfully request withdrawal of this rejection.

In addition, the present invention provides the unexpectedly superior properties of lowering fibrinogen levels without altering coagulation parameters, such as thrombin time and prothrombin time (see Table at pages 18-19). It is well-known in the art that fibrinogen is involved in coagulation; thus, a reduction of fibrinogen should increase bleeding time and

hemorrhagic events. However, Curcuma extract lowers fibrinogen levels without modifying bleeding time. This property is especially useful in the treatment of haemophilic patients.

For example, ticlopidine is used to treat cardiovascular diseases as a fibrinogen reducer, and Ticlopidine can not be administered before or after surgical intervention, because it increases bleeding time (see Desager, *Clin Pharmacokinet.*, 26(5):347-55, 1994, abstract attached hereto). Such has also been shown for other thrombolytic agents (see Hirch, *Chest*, 97 (4 Suppl): 124S-131S, 1990, abstract attached hereto). Further, even statins affect coagulation parameters. After simvastatin or pravastatin administration, recurrent episodes of nose bleeding were observed in some patients (see Panuccio, *Clin Ter,* (5):419-24, 1994, abstract attached hereto).

On the other hand, Curcuma does not modify coagulation parameters other than fibrinogen levels, and this property is evident from the present specification at pages 18-19.

Thus, Applicants assert that the Examiner has applied an improper standard of obviousness, that the cited references do not suggest that Curcumin, or any other compound used for the treatment of cardiovascular disease, on that basis, can be effective to lower fibrinogen levels as claimed, and further, that the claimed invention produces unexpectedly superior properties. Accordingly, Applicants respectfully request that this rejection be withdrawn.

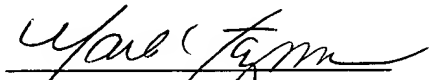
III. Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the

Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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1: Ann Pharmacother. 2001 Feb;35(2):236-41.

Do HMG-CoA reductase inhibitors affect fibrinogen?

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OBJECTIVE: To review commonly used fibrinogen assay methods and the evidence demonstrating an association between fibrinogen and increased risk of coronary artery disease and to review the current literature to determine and assess the impact of hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors on fibrinogen. DATA SOURCES: Primary and review articles identified from a MEDLINE search (1966-December 1999); references obtained from these publications were subsequently reviewed for additional relevant articles. STUDY SELECTION AND DATA EXTRACTION: All articles were evaluated, and all relevant information was included in this review. DATA SYNTHESIS: The Clauss method is currently the preferred method for determining plasma fibrinogen concentrations, due to its high degree of accuracy and precision. Furthermore, unlike immunologic methods, its reliability is unaffected by change in triglycerides. The effects of four HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin, pravastatin) on fibrinogen have been evaluated. Atorvastatin has been shown to induce significant increases in fibrinogen (22% increase; $p < 0.05$) by using the immunonephelometric method. This method also demonstrated that lovastatin use was associated with a 24.4% increase ($p < 0.0001$) in plasma fibrinogen concentration. Simvastatin has been shown in multiple studies using the Clauss method to have a neutral effect on fibrinogen. The majority of studies have revealed significant decreases (7-19%) in fibrinogen following treatment with pravastatin. CONCLUSIONS: Future studies need to be performed evaluating the effects of HMG-CoA reductase inhibitors on fibrinogen, but using direct comparisons and clotting assay methodology.

Publication Types:

- Review
- Review, Tutorial

PMID: 11215845 [PubMed - indexed for MEDLINE]

Clin Pharmacokinet. 1994 May;26(5):347-55. Related Articles, Links

Clinical pharmacokinetics of ticlopidine.

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Platelets contribute significantly to arterial-occlusive thrombosis, one of the major causes of death and disease throughout the world. Consequently, inhibiting platelet function is a potentially important therapeutic goal. Among agents that inhibit platelet function, ticlopidine shows a wide spectrum of antiplatelet activity. There have been a limited number of studies investigating the pharmacokinetic profile of the drug. However, it has been demonstrated that absorption of ticlopidine after oral administration is rapid, is improved when the drug is administered with food, but reduced by the coadministration of antacid. Ticlopidine is extensively metabolised, with little unchanged drug present in the plasma. After administration of a single dose, unchanged ticlopidine can be detected for up to 96 hours postdose. Repeated administration of ticlopidine 250mg twice daily results in 3- to 4-fold accumulation of the drug after 2 weeks. The terminal elimination half-life is between 20 and 50 hours. Dosage selection is not determined by the pharmacokinetic profile of the drug, but rather by determination of the effect of the drug on bleeding time. The clearance of theophylline and phenazone (antipyrine) are reduced by ticlopidine, resulting in increased plasma drug concentrations. In contrast, the plasma concentration of cyclosporin is reduced. Aspirin (acetylsalicylic acid) increases the bleeding time in patients receiving ticlopidine concurrently, while corticosteroids reduce bleeding time. Ticlopidine use is discouraged in patients with severe organ failure. Furthermore, ticlopidine should be discontinued 2 weeks before surgery and dental intervention. Most importantly, the blood cell count should be monitored regularly during the 3 first months of treatment with ticlopidine because 1% of patients receiving ticlopidine may experience agranulocytosis.

Publication Types:

- Review
- Review, Tutorial

PMID: 8055680 [PubMed - indexed for MEDLINE]

: Chest. 1990 Apr;97(4 Suppl):124S-131S. Related Articles, Links

Bleeding time and other laboratory tests to monitor the safety and efficacy of thrombolytic therapy.

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Widespread use of thrombolytic agents in a variety of settings has highlighted the need for measures of safety and efficacy. Previously used laboratory parameters, such as decreasing levels of fibrinogen and increasing levels of fibrin(ogen) degradation products (FDPs), have failed to correlate consistently with hemorrhagic events and have not yet been useful in predicting patients at risk for bleeding. Although the bleeding time (BT) has been considered primarily to reflect platelet function, it also reflects the interaction of platelets with vessel wall and coagulation pathways. Recently, the BT has been considered as a potential predictor of clinical bleeding during thrombolysis. The BT, as a measure of in vivo hemostatic competence, may be particularly well-suited for this application. Serial BTs during thrombolytic therapy may provide valuable information regarding safety and efficacy, but further studies are needed to confirm preliminary findings.

PMID: 2108850 [PubMed - indexed for MEDLINE]

Clin Ter. 1994 May;144(5):419-24. Related Articles, Links

[Treatment of dyslipidemia of the elderly with simvastatin and pravastatin. Effectiveness and tolerance]

[Article in Italian]

Panuccio D, Trabatti MR, Romani A.

Ospedale Simiani Loiano, Divisione di Medicina Generale, USL 22 di S. Lazzaro di Savona.

After reviewing the literature concerning the advisability and efficacy of dyslipidemia treatment in old age, the authors present their experience with the use of HMG CoA reductase inhibitors. Twenty-five patients were treated with simvastatin and 20 with pravastatin. Already after one month of therapy, both drugs had induced a reduction of total cholesterol, LDL-cholesterol, and triglycerides, as well as an increase of HDL-cholesterol. These changes were found to be even more marked after three months of treatment. Altogether, tolerability of both drugs was good. However, recurrent episodes of nose bleeding were observed in two patients with normal blood clotting activity.

PMID: 7924180 [PubMed - indexed for MEDLINE]